Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis

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Intermediate dose low-molecular-weight heparin for thrombosis prophylaxis: systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Background: Different doses of low-molecular-weight heparin (LMWH) are registered and used for thrombosis prophylaxis. We assessed benefits and harms of thrombosis prophylaxis with a predefined intermediate dose LMWH compared to placebo or no treatment in patients at risk of venous thromboembolism (VTE).

Methods: We performed a systematic review with meta-analyses and trial sequential analyses (TSA) following *The Cochrane Handbook for Systematic Reviews of Interventions*. Medline, Cochrane CENTRAL, Web of Science, and Embase were searched up to December 2018. Trials were evaluated for risk of bias and quality of evidence was assessed following the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.

Results: Seventy randomized trials with 34.046 patients were included. Eighteen (26%) had overall low risk of bias. There was a small statistically significant effect of LMWH on all-cause mortality (risk ratio (RR) 0.96; trial sequential analysis-adjusted confidence interval (TSA-adjusted CI) 0.94-0.98) which disappeared in sensitivity analyses excluding ambulatory cancer patients (RR 0.99; TSA-adjusted CI 0.84-1.16). There was moderate quality evidence for a statistically significant beneficial effect on symptomatic VTE (odds ratio (OR) 0.59; TSA-adjusted CI 0.53-0.67; Number Needed to Treat (NNT) 76; 95%CI 60-106) and a statistically significant harmful effect on major bleeding (peto OR 1.66; TSA-adjusted CI 1.31-2.10; Number Needed to Harm (NNH) 212; 95%CI 142-393). There were no significant intervention effects on serious adverse events.

Conclusion: The use of intermediate dose LMWH for thrombosis prophylaxis compared to placebo or no treatment was associated with a small statistically significant reduction of all-cause mortality that disappeared in sensitivity analyses

excluding trials that evaluated LMWH for anticancer treatment. Intermediate dose LMWH provides benefits in terms of VTE prevention while it increases major bleeding.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent cause of morbidity and mortality.[1] Commonly recognized risk factors for VTE in acutely ill patients include age, active cancer, previous VTE, thrombophilia, reduced mobility, recent trauma or surgery, heart and/or respiratory failure, stroke, and sepsis.[2]

The American College of Chest Physicians (ACCP) guidelines recommend the use of mechanical or pharmacological thrombosis prophylaxis for surgical and acutely ill medical patients at high risk of thromboembolism.[3] Multiple pharmacological agents such as unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are available for this indication. Several 'prophylactic doses' are registered for each LMWH type as reflected by differences between authorised summary of product characteristics (SPC) in the United States and Europe, and also by differences in dosing regimens in randomized trials.[4–11] The ACCP guidelines provide no recommendation regarding dose or type of LMWH for thrombosis prophylaxis.

Multiple systematic reviews have evaluated LMWH for thrombosis prophylaxis in specific patient groups, such as oncological patients [12–14], orthopedic patients [11,15], and others.[16–19] While evaluations of risks of bias are vital for any systematic review, these were parsimoniously considered. Further, only one systematic review, in

critically ill patients, used trial sequential analysis (TSA) [17], while the others did not apply any methods to account for risks of random error.[12–19] No review evaluated benefits and harms associated with specifically a low or intermediate prophylactic LMWH dose.

Our aim was to perform a systematic review with meta-analyses and TSA of randomized clinical trials (RCTs) according to *The Cochrane Handbook for Systematic Reviews of Interventions* comparing the benefits and harms of a predefined intermediate dose LMWH versus placebo or no treatment in patients at risk of VTE.[20]

METHODS

This systematic review was conducted according to a prepublished protocol on PROSPERO (CRD42016036951) following recommendations of *The Cochrane Handbook for Systematic Reviews of Interventions* and reported according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) checklist.[20,21]

Eligibility criteria

We considered all RCTs for inclusion irrespective of language, blinding, publication status, or sample size. Quasi-randomized trials and observational studies were excluded. Only trials with adult patients at risk for VTE allocated to intermediate dose LMWH, placebo, or no treatment were eligible for inclusion, regardless their underlying illnesses or setting (hospital or outpatient).

Intervention

All trials that evaluated an intermediate dose of LMWH were considered, independent of the type of LMWH or duration of treatment. If different LMWHs or (weight adjusted) doses were used in one trial or even in one patient, we classified the trial according to what was used most frequently. Trials that evaluated ultra-low-molecular-weight heparin were included as well. We a priori defined 'low' and 'intermediate' dose LMWH in our protocol according to the SPCs as approved by the Food and Drug Administration, the European Medicines Agency and national authorities (Table 1 and Suppl. Table 1).[4–10] The control intervention was either placebo or no treatment.

Outcomes

All outcomes were graded according to the patients' perspective following the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach (Suppl. Table 2).[22] The primary outcome was all-cause mortality at maximum follow-up. Secondary outcomes were serious adverse events (SAE), symptomatic VTE, VTE screening (VTE diagnosed through screening of all patients in the trial), major bleeding, and heparin-induced thrombocytopenia (HIT). SAE was defined as a composite outcome measure summarizing all serious events necessitating an intervention, operation, or prolonged hospital stay according to the *International Council for Harmonisation - good clinical practice guideline*.[23] To assess the balance between thrombosis and bleeding, VTE symptomatic and major bleeding were regarded SAE when they were counted as such by the original trial, but mortality was excluded. VTE included both DVT and PE. A diagnosis of DVT or PE was accepted when confirmed by imaging technique or autopsy. No distinction was

made according to location of DVT. Major bleeding and HIT were registered according to trial criteria, yet HIT required laboratory confirmation.

Search strategy

We searched *the Cochrane Central Register of Controlled Trials (CENTRAL)* in *The Cochrane Library*, *PubMed/MEDLINE*, *EMBASE* and *Web of Science* (Suppl. Table 3). We searched the references of the identified trials and systematic reviews to identify any further relevant trials. Finally, we searched the *World Health Organization trial platform* and *ClinicalTrials.gov* for on-going trials.

Study selection and data extraction

Two authors independently identified trials for inclusion. Any indication for thrombosis prophylaxis was eligible. Trials excluded based on full text were listed with reasons for exclusion. We extracted characteristics of the trials (year of conduct and publication, country, numbers of participating sites and patients enrolled), participants (age, sex, inclusion and exclusion criteria), interventions (type, dose and duration of LMWH), and outcome. Corresponding authors were contacted in case of unclear or missing data. We resolved differences in opinion through discussion.

Bias risk assessment

Two authors independently assessed the risks of bias of the trials according to *The Cochrane Handbook for Systematic Reviews of Interventions*.[20] The following risk of bias domains were extracted from each trial: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. Trials were

classified as having overall low risk of bias if all the domains were assessed at low risk. Trials were considered to have overall high risk of bias if one or more of the bias risk domains were assessed as unclear or high risk of bias.[24]

Statistical analysis

We performed the meta-analyses according to *The Cochrane Handbook for Systematic Reviews of Interventions* using the software package Review Manager 5.3.5.[20] The analyses were performed on an intention-to-treat basis whenever possible. For dichotomous variables we calculated risk ratios (RR) with trial sequential analysis-adjusted confidence intervals (TSA-adjusted CI) if there were two or more trials for an outcome. For rare events (<5% in the control group) we calculated odds ratios (OR) or Peto's OR in case of very rare events (<2% in the control group), each with TSA-adjusted CI. TSA-adjusted CI excluding 1 were considered statistically significant. In case of statistical significant RR we calculated Number Needed to Treat (NNT) or Number Needed to Harm (NNH).

We used a fixed-effect and a random-effects model for meta-analysis in the presence of two or more trials included under the outcomes. In case of discrepancy between the two models, we reported the results of both models. Considering the anticipated abundant clinical heterogeneity, we emphasized the random-effects model except if one or two trials dominated the evidence. Heterogeneity was measured by inconsistency (I^2) and diversity (D^2) and explored by the chi-squared test with significance set at p-value of 0.10.[25,26] We used funnel plots to explore small trial bias if more than ten trials were available.[20]

Trial sequential analysis

TSA is analogue to the interim analysis in a single randomized trial.[27] TSA combines information size estimation for meta-analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance in the cumulative meta-analysis.[28–31] This adjusted threshold is more conservative when data are sparse and becomes progressively more lenient as the cumulated sample size approaches the estimated required information size.[30,32] We performed TSA on all outcomes to account for the risk of type-I error and to provide information on how many more patients need to be included in further trials. Analyses were conducted using TSA software 0.9.5.10 Beta.[33] We performed TSA with an overall type-I error of 5% and a power of 90%. The estimated required information size was calculated using the variance according to the meta-analytic model corresponding to the diversity adjusted information size (DIS), suggested by a relative risk reduction (RRR) of 10%. We calculated the model variance based diversity (D^2) adjusted required information size since the heterogeneity adjustment with I^2 tends to underestimate the required information size.[25] The TSA was conducted using the unweighted control event proportion calculated from the actual meta-analyses. For all outcomes, we reported the CI adjusted for sparse data and repetitive testing, which we described as the TSA-adjusted CI.

Sensitivity analysis

Sensitivity TSA was conducted for all outcomes using a RRR suggested by the meta-analysis of the included trials. If D^2 equalled zero we performed a sensitivity TSA using a D^2 of 25%. Additionally, trials evaluating types of LMWH that we were unable to classify as ‘low’ or ‘intermediate’ were included in sensitivity analyses.

GRADE

We used GRADE to assess the quality of the body of evidence associated with each outcome.[22] The quality measure of a body of evidence considers within-study risk of bias, indirectness, heterogeneity, imprecision, and risk of publication bias.

RESULTS

The search was last updated on December 1st, 2018 and generated 9644 hits (Suppl. Table 4). Screening of reference lists and contacting authors revealed two additional hits. After removing duplicates and screening of titles and abstracts 523 hits remained of which 457 were excluded based on full text. The remaining 66 records reported 70 randomized trials and all fulfilled the eligibility criteria for inclusion. [34–99]

Characteristics of included studies

Two trials were excluded from analyses for reporting surrogate or unclear outcomes.[70,93] Two reports were translated (Chinese and French) [48,95] and six trials were published as abstract only. [37,68,70,85,92,99] Six trials evaluated types of LMWH which we were unable to classify either as ‘low’ or ‘intermediate’ dose; these were excluded from the primary analyses and included in sensitivity analyses as ‘LMWH dose undefined’ (Suppl. Table 5). [35,40,48,60,66] Eventually, 70 trials were included in this systematic review and 68 trials contributed data to the meta-analyses. We identified thirteen ongoing randomized trials (Suppl. Table 6).

There were 36 single-center and 34 multicenter trials (Suppl. Table 7). Two trials used a four-arm design and five trials used a three-arm design; all other trials used a two-arm parallel group design. A variety of types of patients were evaluated by the trials, including ambulatory oncological patients (21 trials), surgical patients (15 trials), orthopedic or immobilized patients (20 trials), acutely ill medical patients (6 trials), neurological patients (3 trials) and others such as pregnant women at high risk of VTE or patients with cirrhotic liver disease (6 trials) (Suppl. Table 7). Eight different types of LMWH were evaluated; enoxaparin and dalteparin were most commonly used (Suppl. Table 7). LMWH was compared to placebo (37 trials) or to no intervention (33 trials). Duration of follow-up varied from 7 days to 5 years.

Bias risk assessment

Random sequence generation was assessed as low risk of bias in 39 trials (54%); allocation concealment in 41 trials (59%); blinding of participants and personnel in 31 trials (44%); blinding of outcome assessors in 38 trials (54%); incomplete outcome data in 49 trials (70%), and selective outcome reporting in 50 trials (71%). A total of 18 trials (26%) were classified as having an overall low risk of bias (Table 2).

Outcomes

For each outcome, the pooled intervention effects with TSA-adjusted CI were calculated, first for the trials with overall low risk of bias, second for all trials irrespective their risk of bias. Further, a priori defined subgroup effects were specified. Detailed data are available for each outcome in the supplementary appendix.

Primary outcome

All-cause mortality at maximum follow-up

Thirty-seven randomized trials with 24,732 patients reported all-cause mortality, with follow-up varying from 7 days to 5 years (Fig 1). Overall mortality proportions were 18.6% in the LMWH group and 19.2% in the control group. The pooled intervention effect estimate of all RCTs suggested an overall beneficial effect in TSA (RR 0.96; TSA-adjusted CI 0.94 to 0.98; I^2 0%; D^2 0%; Table 3) and conventional meta-analysis (RR 0.94; CI 0.90 to 0.98; I^2 12%; Table 3). Control event rates varied from 0.8% (orthopedics) to 76.6% (ambulatory cancer patients) and the overall effect estimate was primarily driven (83.4%) by the subgroup of ambulatory cancer patients receiving LMWH as anticancer treatment (Fig 1). We conducted a sensitivity analysis excluding this subgroup. When considering the remaining twenty-nine trials, TSA was not associated with a lower risk of all-cause mortality in the trials with low risk of bias (RR 1.00; TSA-adjusted CI 0.76 to 1.31; I^2 0%; D^2 0%; Table 3) or in all trials regardless of bias risk (RR 0.99; TSA-adjusted CI 0.84 to 1.16; I^2 0%; D^2 0%; Table 3). Results from conventional meta-analyses and sensitivity analyses confirmed the above results and subgroup analyses on LMWH type, length of intervention period, and length of follow-up showed no statistically significant tests of interaction.

Secondary outcomes

Serious adverse events

Sixteen randomized trials with 10,670 patients reported data on SAE. The incidence of SAE was 4.8% in the LMWH group and 4.2% in the control group. In the trials with overall low risk of bias, 5.4% of the required information size was accrued with low statistical heterogeneity, and no statistically significant intervention effect was found

(RR 1.21; TSA-adjusted CI 0.42 to 3.45; I^2 0%; D^2 0%; Table 3). All conventional and sensitivity analyses confirmed the absence of a significant intervention effect on SAE (Table 3). Subgroup analyses showed no statistically significant tests of interaction.

Symptomatic venous thromboembolism

Thirty-six randomized trials with 24,195 patients reported data on symptomatic venous thromboembolism (Fig 2). The incidence of symptomatic VTE was 1.6% in the LMWH group and 2.9% in the control group. TSA could not be conducted when only including trials with overall low risk of bias since less than 5% of the required information size was accrued. When considering all trials approximately 18.3% of the required information size was reached and a statistically significant beneficial intervention effects was found (OR 0.59; TSA-adjusted CI 0.53 to 0.67; I^2 0%; D^2 0%; NNT 76; 95% CI 60-106; Table 3; Fig 3). These results were confirmed in two out of three sensitivity TSA's and in the conventional analyses of all trials (Table 3). Subgroup analyses showed no significant tests of interaction.

Major bleeding

Fifty-seven randomized trials with 28,182 patients reported data on major bleeding (Fig 4). The incidence of major bleeding was 1.2% in the LMWH group and 0.7% in the control group. TSA could not be conducted since less than 5% of the required information size was accrued (all trials and overall low risk of bias). Conventional analyses of the trials with overall low risk of bias showed no statistically significant increase in major bleeding (Peto OR 1.35; 95% CI 0.81 to 2.26; I^2 3%; Table 3). When considering all trials regardless of bias risk, sensitivity TSA with RRR estimated by the meta-analysis found a statistically significant harmful intervention

effect (Peto OR 1.66; TSA-adjusted CI 1.31 to 2.10; I^2 0%; D^2 0%; NNH 212; 95% CI 142 to 393; Table 3; Fig 5) which was confirmed by conventional meta-analysis (Peto OR 1.66; 95% CI 1.30 to 2.12; I^2 20%; Table 3). No subgroup differences were detected.

Venous thromboembolism screening

Forty-two randomized trials with 13,963 patients reported data on VTE screening. The incidence of VTE screening was 6.3% in the LMWH group and 12.0% in the control group. In the TSA of trials with overall low risk of bias, 5.1% of the required information size was accrued, with moderate statistical heterogeneity, and no statistically significant intervention effect was found (RR 0.57; TSA-adjusted CI 0.14 to 2.32; I^2 52%; D^2 54%; Table 3). The sensitivity TSA with RRR estimated by the meta-analysis found that LMWH was associated with a statistically significant beneficial intervention effect (RR 0.57; TSA-adjusted CI 0.39 to 0.82; I^2 52%, D^2 54%; Table 3). When considering all trials a statistically significant beneficial effect was found (RR 0.52; TSA-adjusted CI 0.44 to 0.61; I^2 0%; D^2 0%; NNT 18; 95% CI 15 to 21; Table 3), confirmed by all conventional meta-analyses and sensitivity analyses. Subgroup analyses based on the duration of the interventions showed a statistically significant test of interaction (p=0.02), indicating a larger beneficial intervention effect in the subgroup of trials treating patients for less than 30 days (RR 0.47; CI 0.42 to 0.53; I^2 0%) compared to the subgroup of trials treating patients for more than 30 days (RR 0.66; CI 0.51 to 0.84; I^2 15%, Suppl. Fig 5c).

Heparin-induced thrombocytopenia

Thirteen randomized trials with 10,340 patients reported data on heparin-induced thrombocytopenia, but no objective laboratory HIT confirmation was reported so we were unable to perform analyses.

Small trial bias

Funnel plots showed no clear arguments for small trial bias in all but one outcome (Suppl. Figure 6a-e). The funnel plot of 'VTE screening' was asymmetric, possibly indicating publication bias.

GRADE approach

The quality of the evidence was assessed as low to moderate for all outcomes based on risk of bias limitations, inconsistency, imprecision and other considerations (Suppl. Table 8).

DISCUSSION

We evaluated the benefits and harms of intermediate dose LMWH for thrombosis prophylaxis in patients at risk for VTE. We included 70 RCTs with 34,046 randomized patients of which 18 trials (26%) had overall low risk of bias. Analyses indicated that compared to placebo or no treatment intermediate dose LMWH was associated with a small decrease in mortality which disappeared in a sensitivity analysis excluding trials that evaluated LMWH for anticancer treatment. Intermediate dose LMWH provides benefits in terms of VTE prevention while it increases major bleeding.

Our findings on mortality are in line with results from previous systematic reviews.[13–17] The overall effect estimate obtained by pooling all RCTs did suggest lower mortality associated with intermediate dose LMWH. However, we decided *post hoc* to do a sensitivity analysis excluding eight RCTs that assessed ambulatory cancer patients who received LMWH as adjuvant to their cancer treatment from the primary outcome analysis as this subgroup had a substantially higher control event rate of mortality of 76.6%, contributed 83.4% weight and was the main driving force for the overall pooled effect estimate and its significance. Although in any meta-analysis a certain amount of clinical heterogeneity is unavoidable, the observed differences in control event rates suggest potentially relevant clinical differences between patient populations. For this reason we deemed it inappropriate to rely solely on the overall pooled effect estimate as this could lead to spurious inferences about the effect on mortality in other subgroups with fewer observed events. This decision was primarily based on clinical considerations as we observed low statistical heterogeneity and subgroup analyses showed no statistically significant tests of interaction.

Robustness of conclusions was evaluated by several additional analyses. We conducted our main analysis with TSA of all outcomes based on an a priori hypothesized 10% RRR as specified in our protocol. Sensitivity analyses with meta-analytic estimates of trials with overall low risk of bias suggested a 41% RRR for symptomatic VTE and a 35% RRI for major bleeding. Although even this low risk of bias RRR estimate may still be overestimated, the a priori specified 10% RRR for the TSA used in our analyses may have been too conservative and alternatively one could probably base the conclusions on the TSA anticipating the RRR estimated from the trials with low risk of bias. Further, in subgroup analyses the bias effect seems

limited since the meta-analytic point-estimates are rather similar across all outcomes regardless of the bias risks of the trials, suggesting that we may rely on the more precise estimates derived from all the trials. These sensitivity and subgroup analyses strengthen the conclusion of a beneficial intervention effect on VTE but also indicate a harmful effect on major bleeding. The NNT for preventing one case of symptomatic VTE is 76 compared to a NNH of 212 for major bleeding, which suggests the balance favors the intervention. As we did not detect any significant subgroup differences we cannot make inferences about the benefit to harm ratio in specific patient populations.

The main strength of this review is its systematic approach according to *The Cochrane Handbook for Systematic Reviews of Interventions*, following a previously published protocol with assessment of the risks of systematic and random errors, and, most important, incorporation of error risks in the primary analyses and conclusions.[20] We systematically explored the associations between bias risks and intervention effects in all outcomes, while previous reviews did not incorporate the bias risks in their results and conclusions.[11,14,15,17]

This systematic review is, however, associated with important limitations. We provided a comprehensive overview of the effects of intermediate dose LMWH in all patient populations. As we wished to evaluate the overall effect of intermediate dose LMWH in patients at increased risk for VTE we deliberately included all types of patients. Generally statistical heterogeneity was low, but obviously clinical heterogeneity of patients, including control event rates, durations of interventions and follow-up was substantial. For reasons described above we made a deviation from

our protocol and decided post hoc, in a sensitivity analysis, to exclude trials which assessed overall mortality in ambulatory cancer patients receiving LMWH as an anticancer treatment from the primary outcome analysis. We did include these trials as planned in analyses of the other outcomes since they also provide data on VTE or major bleeding events.

Second, we included both VTE and major bleeding in our definition of SAE to evaluate the balance between thrombosis and bleeding. While we excluded mortality, our outcome SAE by definition included double counts of VTE and bleeding events since these were also considered separately. Most trial reports were unclear about the definitions and the numbers of SAE and we were often unable to distinguish whether VTE or major bleeding had been incorporated in the SAE counts. This made a direct evaluation of the balance between thrombosis and bleeding impossible. Third, we accepted all events of VTE proven by objective testing, but we did not make a distinction according to DVT location (i.e. distal versus proximal or lower versus upper extremity). This may have contributed to heterogeneity in our VTE outcome definition. However, many of the original trial reports did not provide details on DVT locations, which prevented such detailed evaluations.

Conclusions

The use of intermediate dose LMWH for thrombosis prophylaxis compared to placebo or no treatment was associated with a small statistically significant reduction of all-cause mortality, which however disappeared in a sensitivity analysis excluding trials that evaluated LMWH for anticancer treatment. Intermediate dose LMWH provides benefits in terms of VTE prevention while it increases major bleeding, as

suggested by consistent effects in a broad range of populations estimated by randomized trials with overall low risks of systematic and random errors.

AUTHORSHIP DETAILS

Authors' contributions:

R.J. Eck, W. Bult and F. Keus had full access to all data in the study and take responsibility for integrity and accuracy of data analysis. All authors contributed to study concept and design. R.J. Eck and W. Bult contributed to acquisition of data. R.J. Eck, J. Wetterslev and F. Keus did the statistical analysis and interpreted the data. J. Wetterslev, R.O.B. Gans, K. Meijer, F. Keus and I.C.C. van der Horst provided directions and intellectual content. R.J. Eck and F. Keus drafted the manuscript with critical revisions from all authors. The final version of this manuscript has been read and approved by all authors.

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Potential conflicts of interest disclosure

K. Meijer reports grants from Bayer, Sanquin, and Pfizer; speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS, and Aspen; and consulting fees from Uniqure. J. Wetterslev is a member of the task force at the Copenhagen Trial Unit to develop theory and software of Trial Sequential Analysis. R.J. Eck, W. Bult, R.O.B. Gans, F. Keus and I.C.C. van der Horst report no conflicts of interest.

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Fig 1. Forest plot of all-cause mortality

Fig 1 caption: Forest plot of all-cause mortality at maximal follow-up of LMWH prophylaxis compared to placebo or no treatment in patients at risk for VTE, stratified according to population, including ambulatory cancer patients receiving LMWH for anticancer treatment. *Size of the squares* reflects the weight of the trial in the pooled analysis. *Horizontal bars* represent 95% confidence intervals

Fig 2. Forest plot of VTE symptomatic

Fig 2 caption: Forest plot of VTE symptomatic at maximal follow-up of LMWH prophylaxis compared to placebo or no treatment in patients at risk for VTE, stratified according to the population type. *Size of the squares* reflects the weight of the trial in the pooled analysis. *Horizontal bars* represent 95% confidence intervals

Fig 3. Trial sequential analysis of VTE symptomatic

Fig 3 caption: Trial sequential analysis of VTE symptomatic at maximal follow-up of LMWH compared to placebo or no treatment in patients at risk for VTE. The required information size of 132,001 patients was calculated using the predefined α=0.05 (two sided), β=0.10 (power 90%), D^2=0%, an anticipated relative risk reduction of 10% and an event proportion of 2.86% in the control arm. The cumulative Z-curve is constructed using a random effects model, and each cumulative Z-value is calculated after inclusion of a new trial (as represented by black dots). The dotted horizontal lines represent the conventional naïve boundaries for benefit (positive, Z = +1.96) or harm (negative, Z = -1.96). The etched lines represent the trial sequential boundaries for benefit (positive), harm (negative), or futility (middle triangular area). The

cumulative Z-curve crosses the TSA boundary for benefit, indicating future trials are very unlikely to change conclusions.

Fig 4. Forest plot of major bleeding

Fig 4 caption: Forest plot of major bleeding at maximal follow-up of LMWH prophylaxis compared to placebo or no treatment in patients at risk for VTE, stratified according to the population type. *Size of the squares* reflects the weight of the trial in the pooled analysis. *Horizontal bars* represent 95% confidence intervals.

Fig 5. Trial sequential analysis of major bleeding

Fig 5 caption: Trial sequential analysis of major bleeding at maximal follow-up of LMWH compared to placebo or no treatment in patients at risk for VTE. The required information size of 42,077 patients was calculated using the predefined α=0.05 (two sided), β=0.10 (power 90%), D^2=0%, an anticipated relative risk reduction of -35% (as anticipated by the low risk of bias trials) and an event proportion of 0.7% in the control arm. The cumulative z-curve, constructed using a random-effects model, crosses the TSA boundary for harm, indicating future trials are very unlikely to change conclusions. Please refer to the caption of Fig. 3 for further explanation of the TSA graphic.

Table 1. Classification of low and intermediate dose prophylactic ranges

	A priori defined prophylaxis dose limits		**Dose as used in included trials**
	Low dose	**Intermediate dose**	
Nadroparin (Fraxiparine)	< 5700 IU	≥ 5700 IU	5700 - 7600 IU [a]
Dalteparin (Fragmin)	< 5000 IU	≥ 5000 IU	5000 IU [b]
Enoxaparin (Lovenox)	< 40 mg	≥ 40 mg	40 mg - 1 mg/kg
Tinzaparin (Innohep)	< 4500 IU	≥ 4500 IU	4500 IU [c]
Parnaparin (Fluxum)	< 4250 IU	≥ 4250 IU	Not used
Bemiparin (Zibor)	< 3500 IU	≥ 3500 IU	3500 IU
Reviparin (Clivarin)	< 3436 IU	≥ 3436 IU	Not used

Table 1 footnote: IU: International Units; mg: milligrams; [a] one study by van Doormaal et al[91] used weight-dependent doses up to 15.200 IU intended as prophylaxis; [b] one study by Maraveyas et al[69] used 200 IU/kg intended as prophylaxis; [c] one study by Meyer et al[71] used 100 IU/kg intended as prophylaxis

Table 2. Risk of bias assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Agnelli 1998	Low	Low	Low	Low	Low	Low
Agnelli 2012	Low	Low	Low	Low	Low	Low
Ahuja 2016	Low	Unclear	High	Unclear	Unclear	Low
Alalaf 2015	Low	Low	High	Unclear	Low	Low
AlGahtani 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Altinbas 2004	Unclear	Unclear	High	Low	Low	Unclear
Cesarone 2002	Unclear	Unclear	Unclear	Unclear	high	Low
Chin 2009	Unclear	Unclear	Unclear	Low	Unclear	High
Christensen 2017	Low	High	High	Unclear	High	Low
Conte 2003	Unclear	Unclear	Low	Unclear	Unclear	Low
Dahan 1986	Unclear	Unclear	Low	Unclear	Low	Low
Dar 2012	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Ek 2018	Low	Low	High	Unclear	Low	Low
Elias 1990	Unclear	Unclear	High	Unclear	Low	Low
Fuji 2008a	Unclear	Unclear	Unclear	Low	High	Low
Fuji 2008b	Unclear	Unclear	Unclear	Low	High	Low
Gagneux 1987	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gates 2004a	Low	Low	Low	Low	Low	Low
Gates 2004b	Low	Low	Low	Low	Low	Low
Goel 2009	Low	Low	Low	Low	Low	Low
Haas 2012a	Low	Low	Low	Low	Low	Low
Haas 2012b	Low	Low	Low	Low	Low	Low
Halim 2014	Low	Low	High	Low	Low	High
Ho 1999	Unclear	Low	High	Low	High	Low
Intiyanaravut 2017	Unclear	Low	High	Low	Unclear	Low
Jorgensen 1992	Unclear	Unclear	Low	Unclear	Low	Low
Jung 2018	Low	Low	High	Unclear	Low	High
Kakkar 2004	Low	Low	Low	Low	Low	Low
Kakkar 2011	Low	Low	Low	Low	Low	Low
Kalodiki 1993	Unclear	Low	Low	Low	Unclear	Low
Karthaus 2006	Low	Low	Low	Low	Low	Low
Khorana 2017	Low	Low	High	Low	Low	Low
Kim 2016	Low	Low	Low	Low	High	High
Kiudelis 2010	Unclear	Unclear	High	Unclear	Low	High

Klerk 2005	Low	Low	Low	Low	Low	Low
Kock 1995	Unclear	Unclear	High	Unclear	Low	Low
Lapidus 2007	Unclear	Low	Low	Unclear	Low	Low
Leclerc 1992	Low	Low	Low	Low	Low	Low
Lecumberri 2013	Low	Low	High	High	Low	Low
Lederle 2006	Low	Low	Low	Low	Low	Low
Leizorovicz 2004	Unclear	Unclear	Low	Low	High	Low
Levine 1996	Low	Low	Low	Low	Low	Low
Macbeth 2016	Low	Low	High	Unclear	Low	Low
Maraveyas 2012	Low	Low	High	High	Low	Low
Maurer 2009	Unclear	Unclear	Unclear	Unclear	Unclear	High
Meyer 2017	Low	Low	High	Low	Low	High
Michot 2002	Unclear	Low	High	Low	Low	Low
Modesto-Alapont 2006	Low	Low	High	Unclear	Low	Low
Pelzer 2015	Low	Low	High	High	Low	Low
Perry 2010	Low	Low	Low	Low	Low	Low
Prins 1989	Unclear	Unclear	Low	Unclear	Low	Low
Rodger 2015	Low	Low	Low	Low	Low	Unclear
Rodger 2016	Low	Low	High	Low	Low	Unclear
Samama 1997	Low	Low	Low	Low	Low	Low
Samama 1999	Unclear	Low	Low	Low	Low	Low
Sang 2018	Low	Unclear	High	Unclear	Low	High
Selby 2015	Low	Low	Low	Low	Low	Low
Sideras 2006	Low	Low	High	Unclear	Low	Low
Sourmelis 1995a	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Sourmelis 1995b	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Torholm 1991	Unclear	Unclear	Low	Unclear	Low	Low
Turpie 1986	Unclear	Unclear	Low	Low	Low	Low
Vadhan-Raj 2013	Unclear	Unclear	High	Unclear	Low	Low
van Doormaal 2011	Unclear	Low	High	Low	Low	Low
Verso 2005	Low	Low	Low	Low	Low	Low
Villa 2012	Low	Low	High	Low	Low	Low
Wang 2018	Unclear	Unclear	High	High	Unclear	High
Warwick 1995	Unclear	Unclear	High	Low	Unclear	High
Xia 2011	Low	Unclear	Unclear	Unclear	Low	High
Zwicker 2013	Unclear	Unclear	High	Unclear	Low	Low

Table 2 footnote: Review of authors' judgements about each risk of bias domain for each included study.

Table 3. Outcomes: results from conventional meta-analyses and trial sequential analyses

Outcome	Included trials	Trials (patients)	Conventional analysis [a]	Main analysis TSA [a] *RRR 10%, ß 90%, D^2 model variance based*	Sensitivity TSA [a] *RRR based on low risk trials, ß 90%, D^2 model variance based*	Sensitivity TSA [a] *RRR 10%, ß 90%,D^2 25%*
Mortality						
Including 'LMWH for anticancer treatment'	Low bias risk	10 (10,770)	RR 0.92 (0.86 to 0.98)	RR 0.92 (0.83 to 1.01)	RR 0.92 (0.81 to 1.04)	RR 0.92 (0.82 to 1.03)
Excluding 'LMWH for anticancer treatment'	Low bias risk	8 (10,083)	RR 1.00 (0.89 to 1.13)	RR 1.00 (0.76 to 1.31)	Not performed (RRR 0%)	RR 1.00 (0.73 to 1.37)
Including 'LMWH for anticancer treatment'	All	37 (24,732)	RR 0.94 (0.90 to 0.98)	RR 0.96 (0.94 to 0.98)	RR 0.96 (0.94 to 0.99)	RR 0.96 (0.94 to 0.99)
Excluding 'LMWH for anticancer treatment'	All	29 (20,288)	RR 0.99 (0.90 to 1.10)	RR 0.99 (0.84 to 1.16)	Insufficient data (<5% of DIS)	RR 0.99 (0.82 to 1.19)
SAE						
	Low bias risk	4 (8,741)	RR 1.21 (0.93 to 1.56)	RR 1.21 (0.42 to 3.45)	RR 1.21 (0.68 to 2.14)	Insufficient data (<5% of DIS)
	All	16 (10,670)	RR 1.16 (0.99 to 1.37)	RR 1.16 (0.60 to 2.23)	RR 1.16 (0.91 to 1.47)	RR 1.16 (0.60 to 2.23)
VTE symptomatic						
	Low bias risk	11 (10,759)	Peto OR 0.59 (0.39 to 0.91) [b]	Insufficient data (<5% of DIS) [b]	Peto OR 0.59 (0.30 to 1.18) [b]	Insufficient data (<5% of DIS) [b]
	All	36 (24,195)	OR 0.58 (0.46 to 0.73)	OR 0.59 (0.53 to 0.67)	OR 0.59 (0.48 to 0.73)	OR 0.59 (0.27 to 1.29)
Major bleeding						
	Low bias risk	14 (11,631)	Peto OR 1.35 (0.81 to 2.26) [b]	Insufficient data (<5% of DIS) [b]	Peto OR 1.35 (0.17 to 10.85) [b]	Insufficient data (<5% of DIS) [b]
	All	57 (28,182)	Peto OR 1.66 (1.30 to 2.12) [b]	Insufficient data (<5% of DIS) [b]	Peto OR 1.66 (1.31 to 2.10) [b]	Insufficient data (<5% of DIS) [b]
VTE screening						
	Low bias risk	6 (1,737)	RR 0.57 (0.40 to 0.80)	RR 0.57 (0.14 to 2.32)	RR 0.57 (0.39 to 0.82)	Not performed (D^2 >25%)
	All	42 (13,963)	RR 0.50 (0.44 to 0.57)	RR 0.52 (0.44 to 0.61)	RR 0.52 (0.46 to 0.58)	RR 0.52 (0.43 to 0.62)

Table 3 footnote: ß: power; D^2: diversity; DIS: diversity adjusted information size; OR: odds ratio; RR: relative risk; RRR: relative risk reduction; SAE: serious adverse events; TSA: trial sequential analysis; [a] Small discrepancies of the intervention effect estimates between the traditional RevMan meta-analyses and the TSA adjusted results may occur due to different pooling methods (for example the inclusion of zero-event trials in TSA analyses); [b] Fixed-effect model